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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,070	07/30/2003	David R. Milich	VACCINE-07083	9382

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EXAMINER	
SALVOZA, M FRANCO G	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 08/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,070	MILICH ET AL.	
	Examiner	Art Unit	
	M. Franco Salvoza	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *5 and 20-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-19, 36-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 05/10/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1648, Examiner Salvoza.

2. Claims 1-3, 6-8, 12-15, 18 have been amended. Claims 5, 20-35 have been either canceled or withdrawn. Claims 14 and 15 are drawn to non-elected species. New claims 36-47 have been added.

3. Claims 1-4, 6-13, 16-19, 36-47 are pending and under consideration.

Claim Objections

WITHDRAWN

Claim 17 was objected to as being of improper dependent form for failure to further limit the subject matter of a previous claim. In addition, claim 17 removes the requirement that a heterologous antigen must be present in the composition.

Applicant argues that Claim 1 recites a composition "comprising" particular sequences. While it may include these particular sequences, it may contain additional components. Additionally, claim 17 includes the heterologous antigen and also requires woodchuck hepatitis virus core antigen.

Applicant's arguments are found persuasive, and the objection is withdrawn.

Claim Rejections - 35 USC § 112

MAINTAINED

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 18 and 19 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant argues that after amendments the indefiniteness is resolved.

Applicant's arguments are persuasive in regards to claims 1, 18 and 19.

The rejection is maintained as to claim 2, since the amended claim recites "a loop region comprising residues 76 to 92 of SEQ ID NO: 38." Since the claim recites the word "comprising," it is not clear where the antigen can be inserted within the loop region, which only comprises residues 76-82 but also includes other unspecified residues and locations as well. Claim 8 is newly rejected for the same reasons as the amended claim. Namely, amendment to a "loop region comprising residues 76 to 82."

Therefore, claims 2 and 8 (and claim 3 and 4 dependent on claim 2) are rejected under 35 U.S.C. 112 2nd paragraph.

Claim Rejections - 35 USC § 102

WITHDRAWN

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

> international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-12 and 16-20 were rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication 2003/0138769 A1 to Birkett. Claims 5 and 20 have been canceled, leaving claims 1-4, 6-12, 16-19 rejected under 35 U.S.C. 102(e).

Applicant argues that Birkett fails to teach or suggest how to make and use human hepadnavirus core antigens; Birkett fails to teach or suggest how to make or use hybrid WHcAg particles that are antigenic or suitable for use as vaccines. Furthermore, Birkett teaches the modification of HBcAg by the addition of basic lysine residues to the immunodominant loop of HBcAg, not the present invention requiring modification of WHcAg by addition of at least one acidic amino acid. Additionally, in regards to claims 42-47, Birkett fails to teach or suggest the desirability of hybrid hepatitis virus core particles comprising heterologous antigens having an acidic isoelectric point.

Applicant's arguments are considered but found persuasive. The rejection is withdrawn.

Claim Rejections - 35 USC § 103

MAINTAINED

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 and 16-20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens. Claim 13 was rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens in view of Zlotnick et al.

Claims 5 and 20 have been canceled, leaving claims 1-4, 6-12, 16-19 rejected under 35 U.S.C. 103(a) over Pumpens, and claim 13 was rejected under 103(a) as being unpatentable over Pumpens in view of Zlotnick et al.

Applicants contend that 66% sequence identity is not sufficient motivation to modify or extrapolate the WHcAg sequence disclosed by Galibert et al. with the recombinant HBcAg articles of Pumpens, and while one of skill in the art may find HBc subtypes to be highly conserved, they would not find truncated HbcAg and WhcAg proteins to be highly conserved or interchangeable.

Applicants further contend that a 66% sequence identity does not lead to a reasonable expectation of success, Birkett teaches away, and one of skill in the art would find that the totality of evidence provides an inadequate expectation of success in achieving woodchuck hepatitis virus cores that assemble as hybrid particles, let alone woodchuck hepatitis core particles that are antigenic.

Finally, Pumpens and Zlotnick fail to teach or suggest the insertion of a heterologous antigen at a position chosen from amino acid residues 44, 71, 72, 74, 83, 84, 85 or 92 as required by claim 7, and Pumpens and Zlotnick fail to teach or suggest a truncated WHcAg further comprising any of the C termini.

Applicant's arguments are considered but found unpersuasive.

First, Pumpens teaches strong conservation among hepatitis core antigens (hepatitis; as well as between mammalian core proteins and avian hepadnaviruses) and even more specifically with woodchuck hepatitis core antigens (p. 64, Pumpens; as further supported by US 2003/0138769 A1 in the previous Office Action, and Lew et al. (2001) as cited in the Form 1449 dated Oct. 31, 2003). There is no minimum percentage of homology required between hepatitis core antigens to be interchangeable or not, while 66% indicates more homology than not. In addition the standard is a "reasonable" (emphasis added) expectation of success, not inadequate. Furthermore, applicant's own disclosure posits to some differences, but even alleges they are interchangeable and substitutable and furthermore, woodchuck hepatitis core antigens offer certain advantages.

Second, Pumpens teaches insertions within these ranges (see Tables 1-3, Pumpens). Unless applicant shows unexpected results for insertions at the residue positions recited in the claims, Pumpens is presumed to apply and the rejection stands for reasons of record.

This rejection is extended to new claims 36 and 37, reciting a vaccine comprising a heterologous antigen linked to the amino acid sequence set forth in SEQ ID NO:38; formulated for human administration. It would be obvious to one of ordinary skill in the art that SEQ ID NO:38, which matched the published sequence for WHV as published by Galibert et al. (1982), to use the core molecule as an epitope carrier as described in Pumpens et al. (1995) because of the strong similarity of WHV core antigen to the human counterpart.

One of ordinary skill in the art would have expected to achieve a hepatitis B virus core antigen sequence as an epitope carrier based on the WHV sequence because the techniques involved were well developed at the time of applicant's invention.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 112

NEW, necessitated by amendment

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 42 recites the vaccine of claim 36 wherein the isoelectric point of said heterologous antigen is in the range of 3.0 to 6.0; claim 43 recites the composition of claim 38 wherein the isoelectric point of said heterologous antien is in the range of 3.0 to 6.0; claim 44 recites the vaccine of claim 36 wherein the isoelectric point of said heterologous antigen is in the range of 4.0 to 5.0. Claim 45 recites the composition of claim 38 wherein the isoelectric point of said antigen is in the range of 4.0 to 5.0; claim 46 recites the vaccine wherein the isoelectric point of said antigen is in the range of 3.0 to 4.0; claim 47 further recites the composition of cliam 38 wherein the isoelectric point of said antigen is in the range of 3.0 to 4.0.

The following quotation from section 2163 of the Manual of Patent Examination

Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

In this case, these claims do not require that the antigens possess any particular distinguishing feature, biologic activity, or conserved structure. Therefore, the claims are drawn to a genus of polypeptides that are defined only by a range of isoelectric points. When a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is an antigen with an isoelectric point within specific ranges. There is not even identification of

any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

NEW

Claims 1-4, 6-13, 16, 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antigenic composition comprising an antigen linked to SEQ ID NO:38 wherein said heterologous antigen is inserted at positions such as 44, 73-78 and 81-85, 92 does not reasonably provide enablement for the entire scope of amino acid residues comprising 76 to 82 (in other words, even further components, since the claims comprise 76 to 82 and are not even limited to residues 76-82). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 P 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988) and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Claims 1-4, 6-8 recite an antigenic composition comprising a heterologous antigen linked to SEQ ID NO:38 wherein said antigen and said amino acid sequences assemble as a hybrid particle and wherein said heterologous antigen is inserted at a variety of positions, including within a loop region comprising residues 76-82 of SEQ ID NO:38. The heterologous antigen emcompasses a broad variety of inserts.

Applicant has pointed to references citing hepatitis B core antigen folding and stability problems in particle assembly and steric hindrance created upon insertion of foreign epitopes. (Jegerlehner; Karpenko). Jegerlehner and Karpenko further underscore the high level of unpredictability of chimeric protein self assembly due to complications with foreign amino acid inserts in terms of size, volume, hydrophobicity, high beta strand index, which further restrict the available options. As applicant points out from Jegerlehner in the specification: "less than 50% of foreign epitopes can be accommodated by the HBcAg platform because of adverse effects on particle assembly."

Applicant's disclosure does contain examples of certain inserts at position 78 that have provided stable particle assembly upon C terminal modification (see specification; Tables 11-16 indicating successful particle recovery for specific inserts; satisfactory assembly, immunogenicity). However, the disclosure does not sufficiently teach enough beyond those specific residue positions at 44, 73-78 and 81-85, 92 or specific inserts to enable the entire scope of the cited range and scope of foreign epitopes or antigens. Applicant's own disclosure even teaches a screening method on p. 96 to determine efficacy of expression and assembly of hybrid-core particles at the early bacterial lysate step, in effect indicating that screening is required because of the limited certainty in moving from one species to another.

In view of the breadth of the claims, the lack of examples or guidance, and the fact that those in the art would not be able to determine without extensive experimentation how to create stable insertions within the loop region comprising residues 76 to 82 of SEQ ID NO: 38, the application has not provided sufficient information to enable those in the art to practice the claimed invention without undue experimentation.

NEW, necessitated by amendment

Claims 38-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the rescue of hybrid particles with certain positively charged inserts using flanking glutamic acid residues, does not reasonably provide enablement for other antigenic acidic amino acid additions or substitutions or insertions or substitutions within said amino acid sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 P 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988) and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed

most relevant should be considered.

Claims 38-41 broadly recite the composition of Claim 1, wherein said heterologous antigen further comprises addition of at least one acidic amino acid; wherein said antigen comprises substitution of at least one basic amino acid with at least one acidic amino acid; wherein said amino acid sequence set forth in SEQ ID NO:38 comprises substitution of at least one basic amino acid with at least one acidic amino acid.

Applicant has pointed to references citing hepatitis B core antigen folding and stability problems in particle assembly and steric hindrance created upon insertion of foreign epitopes. (Jegerlehner; Karpenko).

Applicant's disclosure contains examples of the use of flanking glutamic acid residues in Table 18 for specific inserts where the addition of the acidic amino acid residues created successful hybrid particle recovery. However, the disclosure does not sufficiently teach enough beyond that for other acidic amino acid residues (aspartic acid), or for any inserts not specifically mentioned, which comprise a broad variety of antigens and foreign epitopes.

In view of the breadth of the claims, the lack of examples or guidance, and the fact that those in the art would not be able to determine without extensive experimentation how, where, or in what quantities to substitute acidic amino acids to alleviate stability and recovery problems for such hybrid particles, the application has not provided sufficient information to enable those in the art to practice the claimed invention without undue experimentation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to M. Franco Salvoza whose telephone number is (571) 272-8410. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

M. Franco Salvoza
Patent Examiner

Any inquiry concerning this communication or earlier communications from the examiner should be directed to M. Franco Salvoza whose telephone number is (571) 272-8410. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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M. Franco Salvoza
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